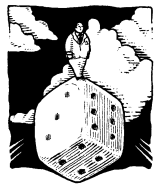
Clinical basics

Prostate cancer: 2. Natural history



Robert K. Nam, MD; Michael A.S. Jewett, MD; Murray D. Krahn, MD, MSc

The case

A 65-year-old man consults his family physician because he is experiencing a frequent and urgent need to urinate. A digital rectal examination reveals a minimally enlarged prostate with no focal nodularity. The level of prostate-specific antigen (PSA) in the patient's serum is higher than the normal range for his age group. Transrectal ultrasound-guided biopsy shows adenocarcinoma of the prostate, with a Gleason score of 6 out of 10 (intermediate grade tumour). Further history-taking reveals that the patient had a myocardial infarction within the past year and that he has mild chronic obstructive pulmonary disease caused by 50 years of smoking. The man is married and sexually active. There is no family history of prostate cancer. The patient is referred to a urologist, who discusses the natural history of prostate cancer and the treatment options (surgery, radiotherapy and watchful waiting), after clinical and radiographic assessment reveals that the lesion is localized to the prostate gland. Unsatisfied, the patient returns to his family physician to request another opinion and more information about his prognosis if he elects not to undergo surgery or radiotherapy.

To address the concerns of the patient described in this case the family physician must consider 3 interrelated questions:

- What is the natural history of adenocarcinoma of the prostate?
- How important is the patient's age, the previous myocardial infarction and the mild chronic obstructive pulmonary disease?
- Is watchful waiting a reasonable strategy for this man? What about delaying surgery or radiotherapy until there is evidence of disease progression?

Natural history of adenocarcinoma of the prostate

What we know about the natural history of prostate cancer comes from case series and cohort studies in which patients with localized prostate cancer received neither surgery nor radiotherapy. This treatment strategy has been termed "watchful waiting," "expectant management" and "conservative management." Since 1980, 16 centres have reported case series of conservatively managed, clinically localized prostate cancer;[1–16] only 3 of these have reported prospectively gathered data.[1,6,12] Most of the studies have reported the prognosis of patients diagnosed with prostate cancer in the 1970s and 1980s. In addition, 2 population-based, retrospective cohort studies have been published.[2,17]

Methods for assessing prognosis

The quality of the methods used in the studies cited varies widely. The re-

This 13-part series was made possible in part by an unrestricted educational grant from ZENECA Pharma

This 13-part series was made possible in part by an unrestricted educational grant from Pharmacia & Upjohn Inc.

Education

Éducation

Dr. Nam is a resident in Urology and a graduate student in Clinical Epidemiology, Division of Urology, Department of Surgery, University of Toronto, Toronto, Ont.; Dr. Jewett is Professor and Chairman, Division of Urology, Department of Surgery, The Toronto Hospital and University of Toronto, Toronto, Ont.; and Dr. Krahn is Assistant Professor, Department of Medicine and Biochemistry, Program in Clinical Epidemiology and Health Services Research Unit, The Toronto Hospital and University of Toronto, Toronto, Ont.

The members of the Prostate Cancer Alliance of Canada, an umbrella group formed to carry out the recommendations of the 1997 National Prostate Cancer Forum, are pleased to support the intent to inform both health care professionals and lay people about the detection, diagnosis and treatment of prostate cancer through this 13-part series. The list of members of the Alliance appears at the end of this article.

Series editors: *Dr. Neill A. Iscoe, Medical Oncologist, Toronto–Sunnybrook Regional Cancer Centre, and Dr. Michael Jewett, Professor and Chairman, Division of Urology, University of Toronto, Toronto, Ont.*

CMAJ 1998;159:685-91

sults of poorly conducted studies, which may report falsely favourable or unfavourable prognoses, must therefore be viewed with caution. Table 1 outlines the key methodologic features of good prognostic studies and highlights those factors of particular importance for studies of prostate cancer.[18]

For any study of prognosis, it is important to identify patients at an early and uniform point in the course of their disease.[18] Because most "watchful waiting" studies of prostate cancer use data gathered retrospectively, it is difficult to ensure homogeneous inception cohorts. Some studies clearly fail this test. For example, one recent high-profile study[3] that reported surprisingly poor prognosis for initially untreated prostate cancer identified patients at a late stage in their disease (time of death), which ensured that slow-growing cancers would be substantially underrepresented.[19,20] Other studies included only incidental tumours found after simple prostatectomy,[9–11,15] and some included a significant proportion of patients with locally invasive and metastatic disease.[4,9,11,15] Finally, in several of the studies[1,3,6,14] cytology, rather than needle core biopsy, was used to diagnose and grade prostate cancer; this method may be associated with overdiagnosis.

Complete follow-up is important because members of an inception cohort who cannot be accounted for may bias the results.[18] In addition, because prostate cancer progresses slowly and outcome events are infrequent, reasonable sample sizes and follow-up periods of 10 to 15 years are necessary to estimate mortality rates accurately. Many of the published studies were small or had insufficiently long follow-up periods.[4,8,12,15]

Defining outcome measures has been a particular problem in studies of prostate cancer. All-cause mortality rates in prostate cancer cohorts are of limited value because the death rates from prostate cancer and from other causes in this largely elderly patient group are of comparable magnitude.[21] Thus, differences in the distribution of coexisting disease in patient cohorts may dramatically affect overall mortality rates and render comparisons between cohorts meaningless. Death resulting directly from prostate cancer (cause-specific mortality) is probably a more objective end-point but is still not without problems. It is not always possible to ascertain the cause of death in patients who had advanced prostate cancer. Published studies often have no explicit criteria for determining that death resulted from prostate cancer;[22] for those that do, the criteria differ from one study to another.[2,3]

Table 1: Key methodologic features of prognostic studies[18]

Assembly of inception cohort*
Description of referral pattern
Achievement of complete follow-up*
Use of objective outcome criteria*
Blind outcome assessment
Adjustment for extraneous prognostic factors*

*Of particular importance in studies of prostate cancer.

When assessing outcome measures, it is important to control for prognostic factors that may have a significant influence on outcome.[18] For clinically localized prostate cancer, histologic grade is one such factor: the prognosis of poorly differentiated disease is significantly different from that for well-differentiated disease.[2] Differences in racial composition,[23,24] genetic differences controlling androgen metabolism[25] and susceptibility to metastasis,[26] smoking rates[27] and even physical activity[28] may also be important in the progression of prostate cancer. Although most studies report prognosis by tumour grade, no studies control for all of these more recently identified factors.

Finally, even the results of methodologically adequate studies may not be easily generalizable to patients in whom prostate cancer is diagnosed today. Most reported data, including that from the 3 prospective studies,[1,6,12] come from patients identified before 1987, when the era of testing for prostate-specific antigen (PSA) began.[29] Earlier cohorts may have presented with later-stage and higher-volume disease than grade-matched post-PSA cohorts. Thus, the prognosis of contemporary patients may be somewhat more favourable.

Results of the prognostic studies

Three studies[2,17,30] meet the minimum methodologic standards (Table 2). In these studies the single most important prognostic factor is histologic grade. In prostate cancer, grade is most commonly determined using the Gleason scoring system,[31] which is based on tumour differentiation and heterogeneity. The Gleason score is the sum of 2 scores of 1 to 5, each for a different area of the tumour. Patients with low-grade (grade 1, Gleason score 2–4) and intermediate-grade (grade 2, Gleason score 5–7) tumours appear to have the best prognosis, whereas the prognosis for patients with high-grade tumours (grade 3, Gleason score 8–10) is substantially worse.

Table 2 also shows 10-year cause-specific survival rates, stratified by tumour grade, from the 3 studies. Our best estimate for patients with untreated, clinically localized prostate cancer is that 9% to 66% will die from prostate cancer within 10 years, depending on histologic grade, the risk increasing with increasing tumour grade. Patients with low- and intermediate-grade tumours have a better prognosis (9% to 13% and 13% to 24% risk of death respectively), whereas patients with high-grade tumours have an unfavourable prognosis (44% to 66% risk

of death). Thus, on the basis of tumour grade alone, the 65-year-old patient described in the case at the beginning of this article has a 13% to 24% probability of dying from prostate cancer within 10 years. However, his true chance of dying from prostate cancer is a little lower, because there is a possibility that he will die from another cause within the next 10 years.

Teaching point

- In thinking about the natural history of prostate cancer, the time horizon should be 10 to 15 years, since follow-up periods of that duration are needed to estimate mortality rates accurately.

Another potentially important prognostic factor is tumour stage[32] (Table 3). Although this is a significant factor in influencing prostate-cancer-specific mortality when all stages of prostate cancer are considered (i.e., localized versus metastatic),[33] differences in stage within clinically localized tumours have not been shown to have independent prognostic value.[2,30] Clinically localized prostate cancer is defined as a tumour confined within the prostate with no evidence of regional or distant metastasis, as assessed by clinical, biochemical and radiographic tests. It is subdivided into tumours that are either nonpalpable by digital rectal examination (stage T1) or palpable but not extending outside the prostate (stage T2). After adjustment for histologic grade, no difference in prostate-cancer-specific survival has been observed for patients with stage T1 and T2 prostate cancer.[2,30]

A final issue to consider is the quality of life of patients living with prostate cancer. For patients treated conservatively, distant metastasis precedes death by a median period of 3 years.[22] The reduction in quality of life associated with advanced disease is substantial and may be as important as the prospect of death in evaluating prognosis.[34]

Effect of age and comorbidity on prognosis

Age may affect prognosis in 2 ways: as a tumour factor and as a host factor. Tumour biology may be different in younger patients.[35] An inherited predisposition to prostate

Table 2: Characteristics of the 3 studies that meet the minimum methodologic standards for assessing the prognosis of clinically localized prostate cancer

Study	Strengths	Limitations	Tumour grade*; 10-yr prostate-cancer-specific survival rate, %		
			1	2	3
Lu-Yao and Yao[17] *(n =18 238)†*	Population-based with specific inclusion and exclusion criteria Large sample size Reports prostate-cancer-specific mortality rate Stratifies prognosis by stage, grade and comorbidity	Retrospective Uses data from an administrative database, which may have inaccuracies in grade, stage and treatment Mean follow-up 4 years	93	77	45
Albertsen et al[2] *(n = 451)*	Population-based with specific inclusion and exclusion criteria and detailed medical chart review Large sample size Mean follow-up 15.5 yr Reports prostate-cancer-specific mortality rate Stratifies prognosis by grade and comorbidity	Retrospective Definition of death from prostate cancer controversial Includes only patients aged 65 to 75 yr	91	76	54
Chodak et al[30] *(n = 828)*	Meta-analysis of 6 studies (2 prospective) Specific inclusion and exclusion criteria/Large sample size Mean follow-up 7 yr Reports prostate-cancer-specific mortality rate Stratifies prognosis by age, stage and grade	4 studies retrospective No detailed medical review	87	87	34

*1 = well differentiated, Gleason score 2–4; 2 = moderately differentiated, Gleason score 5–7; 3 = poorly differentiated, Gleason score 8–10.
†Data derived from the Surveillance, Epidemiology, and End Results (SEER) Program, which collects information on all cancer cases from 5 US states (Connecticut, Hawaii, New Mexico, Iowa and Utah) and 4 US metropolitan cities (San Francisco–Oakland, Detroit, Atlanta and Seattle).

cancer may underlie both presentation at an early age and more aggressive tumour behaviour.[36] Age also affects the probability of dying from other diseases, which has a bearing on the question of whether a patient will live long enough to experience disease and death caused by prostate cancer.

To help illustrate this concept, we have used a model of life expectancy called the DEALE method (declining exponential approximation of life expectancy), in which patient-specific life expectancy is determined from the risks of competing causes of death, including the risk of death from a specific disease (e.g., prostate cancer), the mortality risk from one or more coexisting diseases, and age-, sex- and race-related mortality, which includes mortality risk from all other causes (Fig. 1).[37,38] It is important to recognize that this method involves assumptions, provides only approximate estimates of life expectancy and is used here only to illustrate the potential importance of age and comorbidity in the prognosis of prostate cancer.

Table 3: Current methods of assessing stage of prostate cancer*

Stage	Criteria
T	*Refers to primary tumour; assessed by physical examination, imaging, endoscopy, biopsy and biochemical tests*
T1	Clinically inapparent tumour not palpable or visible by imaging
T1a	Tumour an incidental histologic finding in 5% or less of tissue resected (by TURP)
T1b	Tumour an incidental histologic finding in more than 5% of tissue resected (by TURP)
T1c	Tumour identified by needle biopsy (performed because of elevated PSA, for example)
T2	Tumour confined within the prostate
T2a	Tumour involves 1 lobe
T2b	Tumour involves 2 lobes
T3	Tumour extends through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles or pelvic wall
N	*Refers to regional lymph nodes; assessed by physical examination and imaging*
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	*Refers to distant metastasis; assessed by physical examination, imaging, skeletal studies and biochemical tests*
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph nodes
M1b	Bone(s)
M1c	Other site(s)

Note: TURP = transurethral resection of the prostate, PSA = prostate-specific antigen.
*Adapted from *TNM Classification of Malignant Tumours*, 5th ed. L.H. Sobin and C. Wittekind, editors. Copyright © 1997 Wiley-Liss Inc. Reprinted by permission of Wiley-Liss, Inc., a division of John Wiley & Sons, Inc.

Life expectancy for a man without cancer falls from approximately 22.3 years at age 55 to 9.1 years at age 75.[41] The difference in life expectancy for men with and without cancer provides an estimate of the average number of life years lost because of cancer in men who elect to be treated conservatively. Young men are clearly at highest risk of losing life years to cancer. For 55-year-old men, the loss of life expectancy because of cancer ranges from approximately 2 years for grade 1 disease to over 11 years for grade 3 disease. However, for men at age 75 the number of life years lost is much smaller, ranging from less than 1 year for grade 1 disease to 2 years for grade 3 disease. Clearly, young men with prostate cancer may lose many more potential life years to cancer than older men with disease of comparable grade and have a correspondingly higher risk of dying from, as opposed to with, their cancer.

The other host factor that affects the life expectancy of the patient described in the case is coexisting conditions, in this case, myocardial infarction and mild chronic obstructive pulmonary disease. The best empirical data we have about the effects of comorbidity on life expectancy in patients with prostate cancer is from Albertsen and colleagues.[2] In that study a validated comorbidity index was used to determine the prognostic importance of comorbidity in patients with prostate cancer. Comorbidity was a powerful predictor of overall survival — as powerful as tumour grade. This study illustrated 2 important points. First, comorbidity may pose an even higher risk of death than the cancer itself. Second, life expectancy loss because of cancer is lower in men who have coexisting illnesses. Patients with a high burden of comorbidity are less likely to die from prostate cancer and, therefore, lose fewer years of life to prostate cancer, if they die early from another illness.

Fig. 1 illustrates the same point graphically by means of the DEALE method.[37,38,41] The number of life years lost because of cancer in a patient with coexisting conditions (in this case cardiac and respiratory conditions) is smaller than the number of life years lost because of cancer in a patient without such coexisting conditions. For our model, the specific mortality rates due to cardiac and respiratory disease are based on 10-year survival data for patients who had a myocardial infarction that was treated by thrombolysis and patients who had mild chronic obstructive pulmonary disease.[39,40] Our 65-year-old patient with grade 2 prostate cancer and cardiac and respiratory comorbidity would lose approximately 1.1 years of life expectancy because of the prostate cancer (Fig. 1, grade 2 tumour, line C minus line D), as opposed to about 3.7

years of life expectancy (line A minus line B) if he was as healthy as an average man of his age.

As a final caveat, when data such as these are applied to individual patients, it is important to keep in mind the fact that computing the number of life years lost because of disease does not translate into gains associated with treatment. It would be incorrect to infer, for example, that radical prostatectomy would result in an 11-year gain in life expectancy for a 55-year-old man with grade 3 disease. We still must rely on high-quality empirical evidence from controlled studies (e.g., randomized trials) to obtain reliable estimates of treatment benefit. Because there are no controlled data that reliably estimate the magnitude of treatment benefit associated with surgical and radiotherapy, life expectancy gains resulting from treatment are unknown. The number of life years lost because of cancer is best thought of as a potential upper bound on treatment benefit and probably a substantial overestimate of that benefit for any given patient, since disease recurrence and death occur in a substantial number of patients treated with surgery[42] and radiation.[43]

Teaching points

- The most important tumour-specific variable for predicting prognosis is histologic grade.
- The most important patient-specific factors in predicting prognosis are age and coexisting conditions.
- The choice of therapy should take into account patient preferences for treatment-related outcomes, in addition to survival data.

Watchful waiting versus definitive treatment

What about delaying surgery or radiotherapy until there is evidence of disease progression? As discussed above, our ability to predict which tumours will progress is related to grade and, to a lesser extent, stage for clinically localized prostate cancer. However, we do not yet have reliable clinical or laboratory tools to predict when the disease will progress for a specific patient. There are no data from randomized controlled trials that allow us to evaluate the strategy of delayed curative therapy. At present, observation strategies to monitor disease progression, such as PSA doubling times, are being investigated.[44] However, the role of this strategy remains uncertain, and it should not be considered equivalent to immediate curative therapy.

Even immediate curative therapy for clinically localized prostate cancer, as opposed to watchful waiting, remains controversial. The lack of high-quality evidence from prospective randomized trials comparing radical prostatectomy and radiotherapy with conservative management makes the task of recommending treatment particularly difficult. We must decide who should be treated with watchful waiting on the basis of relatively low-quality, complex data. Our 65-year-old patient presents a difficult treatment choice. We have seen that we must consider 3 factors: tumour grade, age and comorbidity. If our patient was a 75-year-old man with substantial comorbidity and low-grade disease, the decision would be more straight-

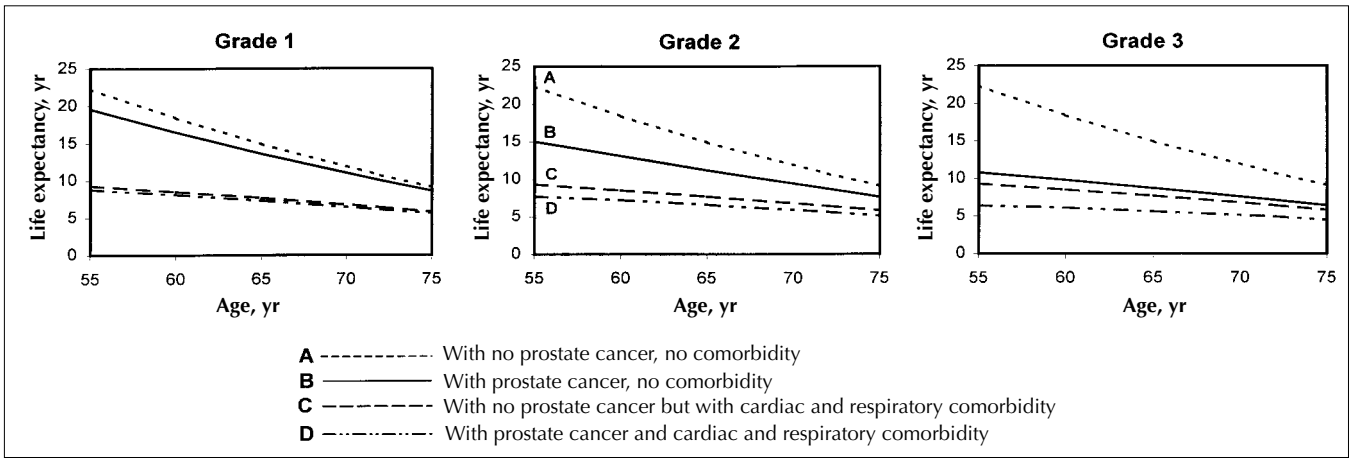


Fig. 1: Patient-specific life expectancy (PSLE) as a function of age and histologic grade of prostate cancer with and without coexisting cardiac and respiratory conditions, based on data from Albertsen and colleagues[2] and the DEALE method (declining exponential approximation of life expectancy).[37,38] PSLE = 1/(Σμ), where μ is the specific mortality rate for prostate cancer, the mortality rate(s) for coexisting conditions(s), and the age-, sex- and race-adjusted mortality rate (ASR). Mortality rates for coexisting cardiac and respiratory conditions are based on 10-year survival rates for patients with myocardial infarction[39] and mild chronic obstructive pulmonary disease,[40] where μ for a patient with myocardial infarction is 0.02039 and for a patient with mild chronic obstructive pulmonary disease is 0.04271. The μ_{ASR} values were obtained from Canadian Life Tables.[41]

forward, and we would probably advise watchful waiting. If he was 55 and otherwise healthy, with high-grade disease, watchful waiting would likely not represent a good choice.

For this particular patient, the decision about which treatment to recommend will depend on what we consider a significant amount of life expectancy lost because of prostate cancer. In other words, is the potential gain in life expectancy of up to 1.1 years if this patient is treated clinically important, if we know that the actual gain will probably be less than that? Naimark and coworkers[45] have suggested that a life expectancy gain of 2 months is significant, given that it corresponds to risk reductions observed in clinical trials widely judged to have clinically significant outcomes. In general, a gain of 6 months has been considered significant by most analysts, a conclusion based on the gains for established treatment interventions such as smoking cessation (10.8 months) and cholecystectomy in asymptomatic diabetic patients (6.1 months).[46] Thus, a loss of 1.1 years from prostate cancer in a patient with substantial comorbidity can be considered clinically significant. However, it remains to be determined whether treatment will translate into a gain of 1.1 years.

Beyond age, grade and comorbidity, there is a fourth important factor: patient preference. Although this issue is not well understood, it is likely that individual patients value outcomes (e.g., sexual and urinary dysfunction) and risks of therapy differently. The morbidity associated with surgical and radiation therapy, including incontinence and impotence, is not trivial and is beginning to be better understood.[47] Some patients are extremely averse to risk and wish to avoid therapeutic complications at all costs. In highly risk-averse patients or those in whom preservation of sexual and urinary function is extremely important, watchful waiting could be considered as a therapeutic option.

Decision-making for patients with localized prostate cancer is clearly not easy. From the available evidence, no concrete recommendation can be made, particularly for the patient described at the outset of this article. We know that we must consider age, histologic grade, comorbidity and personal preference. We have shown that the number of life years lost from prostate cancer in the setting of moderate comorbidity (cardiac and respiratory conditions) can be argued as clinically significant. However, the fact that we cannot guarantee an approximate gain of 1.1 years with treatment makes watchful waiting a reasonable alternative, and we will have to rely heavily on the patient's preference. Presenting the information in an objective, unbiased way, discussing his preferences about treatments and outcomes, and obtaining informed consent to the best of our ability is the most we can hope to achieve, given the present state of the evidence.

References

1. Johansson JE, Holmberg L, Johansson S, Bergstrom R, Adami HO. Fifteen-year survival in prostate cancer: a prospective, population-based study in Sweden. *JAMA* 1997;277:467-71.
2. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. Long-term survival among men with conservatively treated localized prostate cancer. *JAMA* 1995;274:626-31.
3. Aus G, Hugosson J, Norlen L. Long-term survival and mortality in prostate cancer treated with noncurative intent. *J Urol* 1995;154:460-5.
4. Bangma CH, Hop WCJ, Schroder FH. Serial prostate specific antigen measurements and progression in untreated confined (stages T0 to 3NxM0, grades 1 to 3) carcinoma of the prostate. *J Urol* 1995;154:1403-6.
5. Warner J, Whitmore WF Jr. Expectant management of clinically localized prostatic cancer. *J Urol* 1994;152:1761-5.
6. Adolffson J, Carstensen J, Hedlund PO, Lowhagen T, Ronstrom L. Deferred treatment of clinically localized low grade prostate cancer: the experience from a prospective series at the Karolinska Hospital. *J Urol* 1994;152:1757-60.
7. Egawa S, Go M, Kuwao S, Shoji K, Uchida T, Koshiba K. Long-term impact of conservative management on localized prostate cancer. A twenty-year experience in Japan. *Urology* 1993;42:520-7.
8. Zbang G, Wasserman NF, Sidi AA, Reinberg Y, Reddy PK. Long-term followup results after expectant management of stage A1 prostatic cancer. *J Urol* 1991;146:99-103.
9. Stillwell TJ, Malek RS, Engen DE, Farrow GM. Incidental adenocarcinoma after open prostatic adenectomy. *J Urol* 1989;141:76-8.
10. Goodman CM, Busuttil A, Chisholm GD. Age, size and grade of tumour predict prognosis in incidentally diagnosed carcinoma of the prostate. *Br J Urol* 1988;62:576-80.
11. Handley R, Carr TW, Travis D, Powell H, Hall RR. Deferred treatment for prostate cancer. *Br J Urol* 1988;62:249-53.
12. George NJ. Natural history of localised prostatic cancer managed by conservative therapy alone. *Lancet* 1988;1:494-7.
13. Moskovitz B, Nitecki S, Levin DR. Cancer of the prostate: Is there a need for aggressive treatment? *Urol Int* 1987;42:49-52.
14. Larson A, Norlen BJ. Five-year follow-up of patients with localized prostatic carcinoma initially referred for expectant treatment [abstract]. *Scand J Urol Nephrol* 1985;19:30.
15. Cantrell BB, DeKlerk DP, Eggleston JC, Boitnott JK, Walsh PC. Pathological factors that influence prognosis in stage A prostatic cancer: the influence of extent versus grade. *J Urol* 1981;125:516-20.
16. Jones GW. Prospective, conservative management of localized prostate cancer. *Cancer* 1992;70:307-10.
17. Lu-Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer. *Lancet* 1997;349:906-10.
18. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical epidemiology: a basic science for clinical medicine*. 2nd ed. Toronto: Little, Brown; 1991.
19. Abrahamsson PA, Adami HO, Taube A, Kim KM, Zelen M, Kulldorff M. Re: Long-term survival and mortality in prostate cancer treated with noncurative intent [letter]. *J Urol* 1996;155:296-8.
20. Chodak GW. What to expect from prostate cancer [editorial]. *J Urol* 1995; 154:2132-3.
21. Lepor H, Kimball AW, Walsh PC. Cause-specific actuarial survival analysis: a useful method for reporting survival data in men with clinically localized carcinoma of the prostate. *J Urol* 1989;141:82-4.
22. Chodak GW, Vogelzang NJ, Caplan RJ, Soloway MS, Smith JA. Independent prognostic factors in patients with metastatic (stage D2) prostate cancer. *JAMA* 1991;265:618-21.
23. Ross RK, Coetzee GA, Reichardt J, Skinner E, Henderson BE. Does the racial–ethnic variation in prostate cancer risk have a hormonal basis? *Cancer* 1995;75:1780.
24. Optenberg SA, Thompson IM, Friedrichs P, Wojcik B, Stein CR, Kramer B. Race, treatment, and long-term survival from prostate cancer in an equal-access medical care delivery system. *JAMA* 1995;274:1599-605.
25. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1996;88:1118-26.
26. Dong JT, Lamb PW, Rinker-Schaeffer CW, Vukanovic J, Ichikawa T, Isaacs JT, et al. KAI1, a metastasis suppressor gene for prostate cancer on human chromosome 11p11.2. *Science* 1995;268:884-6.
27. Rodriguez C, Tatham LM, Thun MJ, Calle EE, Heath CW. Smoking and fatal prostate cancer in a large cohort of adult men. *Am J Epidemiol* 1997; 145:466-75.

28. Lee IM, Paffenbarger RS, Hsieh CC. Physical activity and risk of prostatic cancer among college alumni. *Am J Epidemiol* 1992;135:169-79.
29. Stamey TA, Yang N, Hay R, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987;317:909-15.
30. Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med* 1994;330:242-8.
31. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol* 1974;111 (1):58-64.
32. Urological tumours. In: Sobin LH, Wittekind C, editors. *TNM classification of malignant tumours*. 5th ed. New York: Wiley-Liss, Inc.; 1997. p. 170-3.
33. Mettlin C, Jones GW, Murphy GP. Trends in prostate cancer care in United States, 1974-1990: observations from the patient care evaluation studies of the American College of Surgeons Commission on Cancer. *CA Cancer J Clin* 1993;43:81-91.
34. Da Silva FC. Quality of life in prostatic cancer patients. *Cancer* 1993;72:3803-6.
35. Gronberg H, Damber JE, Jonsson H, Lenner P. Patient age as a prognostic factor in prostate cancer. *J Urol* 1994;152:892-5.
36. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci U S A* 1992;89:3367-71.
37. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy: 1. Validation of the method. *Am J Med* 1982;73:883-8.
38. Beck JR, Pauker SG, Gotlieb JE, Klein K, Kassirer JP. A convenient approximation of life expectancy (the "DEALE"): 2. Use in medical decision-making. *Am J Med* 1982;73:889-97.
39. Mark DB, Hlatky MA, Califf RM, Naylor CD, Lee KL, Armstrong PW, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *N Engl J Med* 1995;332:1418-24.
40. Burrows B, Bloom JW, Traver GA, Cline MG. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *N Engl J Med* 1987;317:1309-14.
41. Statistics Canada. Life tables: Canada and provinces. *Health Rep* 1990;2:17.
42. Gerber GS, Thisted RA, Scardino PT, Frohmuller HG, Schroeder FH, Paulson DF, et al. Results of radical prostatectomy in men with clinically localized prostate cancer. *JAMA* 1996;276:615-9.
43. Duncan W, Warde P, Catton CN, Munro AJ, Lakier R, Gadaila T, et al. Carcinoma of the prostate: results of radical radiotherapy (1970–1985). *Int J Rad Oncol Biol Phys* 1993;26:203-10.
44. Nam RK, Klotz LH, Jewett MAS, Danjoux C, Trachtenberg J. Prostate specific antigen velocity as a measure of the natural history of prostate cancer: defining a "rapid riser" subset. *Br J Urol* 1998;81:100-4.
45. Naimark D, Naglie G, Detsky AS. The meaning of life expectancy: What is clinically significant gain? *J Gen Int Med* 1994;9:702-7.
46. Krahn MD, Naglie G, Naimark D, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 4. Analyzing the model and interpreting the results. *Med Decis Making* 1997;17:142-51.
47. Lim AJ, Brandon AH, Fiedler J, Brickman AL, Boyer CI, Raub WA Jr, Soloway MS. Quality of life: radical prostatectomy versus radiation therapy for prostate cancer. *J Urol* 1995;154:1420-5.

Reprint requests to: *Dr. Murray D. Krahn, Department of General Internal Medicine, The Toronto Hospital, 200 Elizabeth St., Room ENG-248, Toronto ON M5G 2C4; fax 416 595-5826*

The following organizations are members of the Prostate Cancer Alliance of Canada: Canadian Association for Nurses in Oncology, Canadian Association of Radiation Oncologists, Canadian Cancer Society (National), Canadian Prostate Cancer Network, Canadian Prostate Cancer Research Foundation, Canadian Urology Association, Canadian Uro-Oncology Group and National Cancer Institute of Canada.